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NORMAL SLEEP PATTERNS IN THE MACAQUE MONKEY

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Introduction

The purpose of this paper is to attempt a more complete definition of the normal sleep pattern of the monkey <u>Macaca nemestrina</u>, and to investigate the electrical activity of the cortex and of various deep brain structures during sleep, by means of the electroencephalogram and the averaged evoked response to a sound stimulus.

The majority of neurophysiological studies on sleep during the last few years have been primarily concerned with the cat. Lately, however, there has arisen some evidence that certain differences exist between sleep in the cat and sleep in the subhuman primate,[1,25] suggesting that, by phylogenetic affinities to man, other primates may assist materially in the elucidation of human sleep mechanisms.

Extensive work has been carried out on the neurophysiology of sleep in the cat.[7,16,17,29] The natural sleep of cats is divided by most observers into two basic stages.[7,22] The first is one of generalized electrical slow waves starting in the cortex and then invading the diencephalon and mesencephalon. This is associated with a drop in pulse, regular respirations, and a slight drop in neck muscle tone. The second stage is the so-called paradoxical stage and is accompanied by fast, low voltage EEG activity in the cortico-mesodiencephalic structures, while in limbic regions such as the dorsal hippocampus there is 5 cps rhythmic activity similar to that often seen during wakefulness, and regular 6 to 8 cps spindling activity occurs in the pontine reticular formation. This electrical activity is accompanied by rapid eye movements (REMs) and other easily recognized physiological concomitants.[18,23]

Jouvet[16,17] believes the neocortex to be necessary for the slow wave

stage of sleep, since its subcortical manifestations cannot be detected after total neocortectomy, although the paradoxical phase is unaffected. He also believes the neural tissue necessary for the production of the paradoxical stage resides in the pontine reticular formation, specifically the nucleus reticularis pontis oralis and nucleus reticularis pontis caudalis. Coagulation of this tissue will prevent the paradoxical phase from occurring during sleep, although low voltage fast activity while awake is not modified. Jouvet postulates that the limbic-midbrain system[2,21] may be involved as a discharge pathway.

The normal scalp EEG of the monkey <u>Macaca mulatta</u> has been studied from a developmental standpoint by Caveness, but this did not include consideration of paradoxical sleep or of the normal sleep pattern.[5,6] Caveness characterized sleep other than drowsy in two stages, light and deep. In light sleep he found spindles disappearing with an increase in age, while deep sleep was characterized generally by high voltage slow activity.

The first report of low voltage fast (LVF) activity associated with REMs during sleep in the monkey was by Weitzmann in 1961, who studied the rhesus monkey with chronic cortical and subcortical electrodes.[30] He was unable to characterize the normal sleep pattern, because the experimental situation required frequent interruption of sleep. However in a total of eight hours sleeping time in three monkeys, LVF activity with REMs was seen for a total of 89 minutes, or 16% of the time. The longest observed period of uninterrupted sleep was 45 minutes.

There has been little published on subcortical activity of the monkey during sleep. Hodes and Heath (1952) recording in the rhesus from cortical

and subcortical structures, including the caudate nucleus, reported sub-cortical slowing preceding cortical slowing in the onset of natural sleep.[13]

Studies in progress in the chimpanzee indicate that the general pattern of sleep is similar to that found in man, and that, in contrast to the cat, hippocampal rhythms fail to show reciprocal rhythms with the cortex. It has been suggested that there may be limbic mechanisms of sleep control in primates not seen in lower animals.[1,26,27]

Method

Six young adult (7 to 8 lb.) pigtail macaque monkeys Macaca nemestrina were studied for a total of 20 all night sessions. All animals had chronically implanted bipolar electrodes of 26 gauge stainless steel tubing spaced 2 mm apart, epoxy varnished and stereotaxically placed in the amygdalae, hippocampi, nucleus centrum medianum, and nucleus reticularis pontis caudalis. Stainless steel skull screws were used for bilateral frontal, temporal, parietal, and occipital cortical leads in each animal. Electro-oculograms were recorded from silver disc electrodes on the skin above and lateral to the orbits. The animals slept in a sound attenuated, air conditioned room and were partially immobilized in a restraining collar. They were constantly monitored on closed circuit TV.

Electroencephalograms were recorded at 15 mm/sec on an eight channel Grass model 6 electroencephalograph, and also on a seven channel Ampex tape recorder at 1 7/8 ips. In certain instances, 16 EEG channels and 14 tape channels were recorded for simultaneous observation of all leads. Clicks were delivered continuously at four second intervals (square wave pulses of 0.5 msec duration) to a speaker adjacent to the animal. The animal's

position relative to the sound source was maintained by the restraining collar so that head rotation was limited to $\pm$ 15 degrees. Timing for click voltage, and tape and EEG stimulus markers, was controlled by Tektronix waveform generators triggering a series of pulse generators. An automatic coder was used to sequentially number two minute epochs on both tape and paper records in binary decimal code throughout the night.

Averaged evoked responses to click were computed with a CDC 160-A general purpose digital computer, which averaged 50 responses and graphically displayed the average on a six inch graph representing two seconds of real time.

Histology is not yet available as these animals are being used in further experiments involving lesions of various deep structures.

Results

Although there is not general agreement on categorization of sleep into stages on the basis of the electroencephalogram, our review of these sleep records indicates that it is possible to divide normal sleep in the monkey into broad electrical categories. Where possible, these have been related to behavioral data. On the basis of electrical and behavioral characteristics, we have recognized the following stages of sleep and wakefulness: (1) awake, (2) drowsy, (3) light sleep, (4) intermediate sleep, (5) deep sleep, and (6) paradoxical sleep.

The awake record (Fig 1, top), was characterized by fast, low voltage activity in all leads, with varying amounts of alpha activity.

The term drowsiness as used here is that period between the end of electrical and behavioral alertness and the onset of electrical light sleep.

The animal was motionless, with eyes closed, although there were occasional blinking movements. The EEG pattern was basically one of fast activity, but synchronization was more prominent than in the awake record. There were varying amounts of 12 cps cortical rhythmicity, and prominent 11 to 12 cps spindling activity was seen in the hippocampus, which was occasionally but not necessarily associated with the cortical rhythmicity (Fig 2, top).

Light sleep (Fig 2, bottom) included those epochs that did not fit into categories of drowsy, intermediate, deep, or paradoxical sleep. Its general characteristics varied with the time of night, the record decreasing in amplitude in the morning hours by comparison with the early part of the night. The cortical record was one of low to medium voltage slow 2 to 3 cps activity, with some overlying LVF activity in the frontal leads. Deep structures retained much low to medium voltage fast activity, especially the amygdalae and pontine reticular formation. Occasional 11 to 12 cps spindling activity was noted in the hippocampus, similar to that seen in the drowsy state. There were frequent head and body movements with EEG shifts to low voltage patterns during this stage of sleep.

Intermediate sleep was defined primarily on the basis of the cortical record, which resembled light sleep with prominent 2 to 3 cps activity of moderate to high voltage, but most of the underlying LVF activity had disappeared (Fig 3, top). There were also frequent high voltage 1 to 2 cps waves occurring singly or in short trains, more prominent in the frontal leads, in less than 50% of the record. The amygdalae reflected this slow activity more prominently than other deep structures. Intermediate sleep occurred most commonly before the animal entered deep sleep; it was rarely

seen as a recognizable entity in emergence from deep sleep. The animal was usually motionless during this stage, and its rare movements were associated with the shifting of the EEG toward lighter sleep.

In deep sleep, the cortical record was composed of more than 50% high voltage slow activity at around 1 cps from both anterior and posterior leads, but more obvious frontally (Fig 3, bottom). In the reticular formation, slow waves occurred at approximately 2 to 3 cps, with LVF activity superimposed. The animal was motionless during sleep, but shifts in position or other movements often seen at the termination of an epoch of deep sleep were associated with EEG changes towards light sleep. There were occasional slow rolling eye movements in this deep phase.

The EEG during paradoxical sleep was generally of low voltage fast activity in all areas, but somewhat more rhythmical and slower than the awake record (Fig 1, bottom). In addition to the LVF activity, the frontal cortex showed prominent 4-8 cps rhythms, while in the posterior cortex there were slower, irregular rhythms at 2 to 4 cps. In this period of LVF activity there were characteristic large, rapid, conjugate eye movements (REMs) seen through the closed or more rarely partially opened lids, and occasional facial twitches. The animal was otherwise motionless during the characteristic paradoxical EEG state. A single epoch of paradoxical sleep was characteristically interrupted every few minutes by body movements and altered EEG patterns described below.

Total sleep time from two representative nights for each animal was used to determine the average time spent in various stages of sleep (Fig 4). The majority of sleep (48.7%) was within the light stage,

drowsy states comprised 14.6%, deep sleep averaged 13.6%, intermediate sleep 12%, and paradoxical sleep 11.1%.

A representative night's sleep pattern is illustrated in Fig 5. This curve has been smoothed to eliminate minor EEG shifts from one stage to another that occurred during the night, but rather illustrates major shifts and the overall cyclic pattern. Some of the awakenings resulted from unavoidable laboratory noise, but others appeared spontaneously. Deep sleep characteristically occurred early, usually prior to the first paradoxical period. Most of the night's deep sleep was in the first half of the night, whereas most of paradoxical occurred during the early morning hours. As illustrated, paradoxical sleep can occur during either the ascending or the descending portion of the sleep cycle.

One type of electrical shift observed during an arousal from deep sleep by accidental laboratory noise is shown in Fig 6. The noise occurred 2 to 3 seconds before the arrow indicating opening of the eyes and there was an immediate increase in LVF activity in the pontine reticular formation. This was followed by a generalized increase in frequency in deep structures, and then the eyes opened. The cortical record retained much slow activity, although the animal was looking around and moving. After several seconds, slow high voltage activity was again noted in the amygdalae associated with the cortical slow activity, and an awake record appeared only after a further 10 seconds.

It is of interest that during an arousal from deep sleep such as illustrated here, the animal appeared from a behavioral standpoint to be transiently disoriented. This was in contrast to a sudden arousal from

paradoxical sleep where the animals appeared alert almost immediately. This observation would seem to have implications relating to the depth of sleep, and would seem not to support the hypothesis that paradoxical sleep is indeed 'deeper' sleep.

The EEG patterns in paradoxical sleep are shown in Fig 7, with a drowsy record for comparison. Shortly after the cessation of eye movements, the 11 to 12 cps hippocampal spindling characteristic of drowsiness appeared with associated 12 cps cortical rhythmicity. The animal usually moved (arrow), and opened his eyes briefly. This EEG pattern persisted for 20 to 40 seconds, and then the cortical rhythmicity and hippocampal spindling disappeared with re-emergence of the REMs. Such an interruption might terminate a period of paradoxical sleep, though it need not. More often the paradoxical epoch merely blends into light sleep.

The averaged evoked response to click was computed for all electrode sites during all sleep stages for all animals. The averaged evoked response for each structure showed considerable similarity in identical sleep stages for a particular animal, but varied in basic configuration from animal to animal, both as a function of electrode placement and from individual differences. However, essential characteristics of responses in each stage of sleep were seen in all animals.

Fig 8 shows the characteristic changes in the averaged evoked response to click in relation to the stage of sleep in one animal. The most notable cortical changes occurred in those anterior leads that include a temporal reference and may be due to proximity to auditory cortex.

In general, the latency of the primary component did not vary

significantly during the various sleep stages, though its amplitude and configuration might vary, as during the progression from awake through drowsiness to light sleep. The most prominent changes occurred during deep sleep in the hippocampi and neocortex, with an increase in amplitude and duration of the response, and in the cortex, with addition of prominent high amplitude secondary and tertiary components. During paradoxical sleep, responses were greatly reduced, with loss of secondary components. The response in the amygdalae disappeared during paradoxical sleep, whereas the hippocampal response was slightly larger than during the awake state. The response in the pontine reticular formation persisted during paradoxical sleep and showed little significant deviation from the response seen in other stages.

Discussion

Sleep in the monkey, and in primates generally, is more complex from the standpoint of the various "stages" or "types" than sleep in lower species. The criteria developed here basically resemble those proposed by Dement and Kleitman for human sleep.[8,9] This is in contradistinction to the cat, for example, where sleep seems to be but of two types, mixed spindle-slow wave, and paradoxical.

Sleep in the monkey and man is also similar in its general cyclic nature. Although the length of the cyclic period in the monkey has not yet been accurately determined, it would not appear grossly dissimilar to the 85 to 90 minute cycle in man, and certainly much longer than the 20 to 30 minute periodicity in the cat.

Animals were occasionally awakened by adventitious noise in the

laboratory, but more often would appear to awaken spontaneously. The time elapsing before return to sleep would vary from a minute or two to as long as an hour, and was not clearly related to the type of awakening, either induced or spontaneous. The unrestrained monkey will sleep curled up on the floor of his cage or in a partially supported sitting position, whereas the monkeys in this study slept by necessity in a sitting position with a restraining collar to prevent manipulation of their EEG cables. However the collar was only slightly modified from that in which they were normally restrained for several weeks to months. Steroid studies have indicated easy adaptation to this confinement[33] so that its influence on their sleep pattern appeared minimal. The normal sleep pattern of the unrestrained animal must be investigated before this problem can be resolved.

Associated with the foregoing question of frequent awakenings are the episodes during which the animal would open his eyes briefly during deep sleep and look around, and then close his eyes, with little or no associated EEG change. It seems highly unlikely that the animal is actually awake during these episodes, but rather that the eye opening is an incidental motor phenomenon. Brief eye opening with the preservation of the sleep EEG and no other behavioral indication of wakefulness has also been noted in man[24] and in the monkey by Weitzmann.[31]

Although Hodes et al[13] reported that, with the onset of sleep, slow activity was first seen subcortically, the present study is equivocal in this respect. With progression from drowsiness to deep sleep, there was variability in the first appearance of high voltage slow activity in cortical or deep leads. However, as sleep lightened and the animal

awakened, faster, low voltage activity appeared first in the reticular formation, then in other deep structures, and finally in cortical leads. It is possible that differences in technique or placement account for the different findings, since our results agree generally with those of Weitzmann.[31]

The averaged evoked responses to click in this study were in certain respects similar to those reported by Williams in man.[32] The prominent late high amplitude slow components that occur during deep sleep in the monkey are also seen in the human cortex during stage 3 and stage 4 sleep. The marked diminution of all components that occurs with paradoxical sleep in the monkey is also seen in man. In Williams' study, however, the awake stage had the highest amplitude averaged evoked response.

In this study, the pontine reticular formation response in two animals was large and of short duration, suggesting that the electrode may be near a primary sensory pathway, although current work indicates that this response is dependent upon intact connections with the amygdala. It is of interest that a great variability in the evoked response to click in the mesencephalic reticular formation of the chimpanzee has been noted during paradoxical sleep,[27] and Allison, correlating the evoked response with the presence of eye movements during paradoxical sleep in cats, found that lemniscal responses increased in the presence of eye movements, while extra-lemniscal responses simultaneously decreased.[3] The slight differences noted in the pontine reticular formation responses during the various stages of sleep in this study are probably not significant.

Although the various stages of sleep, as defined by EEG activity, are

clearly separable from each other when the characteristic pattern is fully

developed, the difficulty of establishing the transition point remains.

The point, for instance, at which drowsiness becomes light sleep, or light

sleep becomes intermediate sleep, cannot be isolated. This has been

interpreted to indicate that sleep is a neurophysiological continuum, but

such is not necessarily the case. Equally valid explanations may be offered

from a consideration of the complex changes in responses of different

cortical-subcortical systems at different levels of sleep, and the mutual

interdependence of these systems. The apparent neurophysiological unique-

ness of the paradoxical stage as shown by lesions in the nuclei pontis

caudalis and oralis would support such a thesis, as would the work of Naquet,

et al[20] showing a reduction of spindle activity from thalamic lesions.

It will be noted that the percentage of paradoxical sleep reported in

this study is considerably lower than that reported for man, the cat, and

other primates. Weitzmann reported 16% paradoxical sleep in the monkey.

There are several possible reasons for this difference. In this study the

animals were observed continuously from about 5 PM to 7:30 AM the next

morning, in an effort to record the total amount of sleep for that 24 hour

period. There is reason to believe that such was the case, as the animals

were caged in a busy laboratory during the day, and were not observed to

sleep. By designing the experiment in this way, more drowsy and light

sleep may have been included, thus lowering the percentage of paradoxical.

It is also relevant that the criterion of paradoxical sleep was not

established on the basis of the EEG alone, but also required the presence

of rapid eye movements. In man, REMs are not found during the entirety

of a paradoxical epoch established from EEG and other criteria, and it might be assumed that such is the case in sub-human primates. With REMs as an essential requirement, it is not unlikely that some paradoxical sleep was grouped with drowsy or light in calculating these ratios. The rhythmical cortical record that was usually seen during paradoxical sleep was interesting in that Kleitman has found slow cortical rhythmicity during paradoxical sleep in humans to correspond in time to on-going dream imagery.[19]

Since the nuclei reticularis pontis oralis and caudalis have been shown to be important in the production of paradoxical sleep in the cat, the question of their relationship to paradoxical sleep in the primate is important. The prominent 6-8 cps spindling activity seen in these nuclei in the cat has not been seen in the monkey, nor can it be said that there is a specific activity pattern in these nuclei that is characteristic of paradoxical sleep. It is interesting that during transient interruptions of paradoxical sleep of the type illustrated in Fig 7, the activity of the pontine reticular formation is faster and of lower voltage during the interruption than during the REM part of the record. Huttenlocher, studying single units in the mesencephalic reticular formation of the cat, found the spontaneous discharge rate during paradoxical sleep to be higher than in either slow wave sleep or the awake state, although the discharge pattern during paradoxical sleep varied somewhat more.[14,15] Unit activity in the pontine reticular formation has not yet been studied.

Although Jouvet and others have produced paradoxical sleep in the cat by stimulation of the pontine reticular formation, Weitzmann and his group have not been able to duplicate this in the monkey.[31]

Thus available evidence seems to indicate that the pontine reticular formation is not as intimately related to paradoxical sleep in the primate as it is in the cat, and perhaps lower species in general. This supports the hypothesis, advanced on the basis of work in the chimpanzee, that there may be a higher level of sleep control in the primate.[1,26]

The relationship of eye movements to paradoxical sleep is unclear. Since the nuclei responsible for eye movements are anatomically related to the pontine reticular formation, it has been postulated in the cat that the activity of this part of the reticular formation during paradoxical sleep acts on the adjoining motor nuclei at the same time and so induces discharges which result in eye movements. However, since no special activity is seen, with macroelectrodes, in the pontine reticular formation of primates during paradoxical sleep, it is difficult to evaluate this aspect. In man, REMs have been found to correspond in incidence and direction with the dream imagery.[10,11,28] This suggests that eye movements may be controlled or modulated by cortical activity, or a lower center must be implicated in controlling both. There is also evidence however that rapid eye movements are found during paradoxical sleep in the congenitally blind,[4] in which case the dream imagery is not visual. Thus the rapid eye movement may be a vestigial accompaniment of paradoxical sleep in man which is seen even if the psychic content of the dream contains no visual imagery, and which is possibly determined by activity of lower structures as a function in common with animals lower on the phylogenetic scale.

Epstein[12] has advanced the hypothesis that recurrent dreams, in certain patients with temporal lobe seizure disorders, are themselves

manifestations of an abnormal cerebral discharge, probably arising in the temporal areas. Should this be true, it would indicate that paradoxical sleep complete with REMs can be triggered by the activity of temporal lobe structures, and would tend to support the hypothesis that the limbic system may be superimposed on a phylogenetically older pontine system for the production of paradoxical sleep in primates.

Summary

Normal sleep patterns of the Macaca nemestrina monkey were studied in six subjects for 20 nights. Bipolar EEG records were secured from surface and deep electrodes. Eye movements were monitored by EOG and by closed-circuit TV. Clicks were continuously presented at four second intervals. EEG records were divided into the following stages: awake, drowsy, light, intermediate, deep, and paradoxical. Sleep phases were cyclic, with cycle durations of 75 to 85 minutes, thus resembling human sleep, but the longest segments of deep sleep occurred in the early part of the night. Paradoxical phases occurred during the latter half of the night. Awakening during the night was usually correlated with an initial shift to fast activity in the pontine reticular formation, followed by changes in other deep structures, and lastly, if at all, in cortical areas.

Footnote

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Legends to Figures

Fig. 1. A. Normal waking record prior to sleep. Note eye movement artifacts reflected in cortical leads. B. Paradoxical sleep with REMs. Abbreviations: RF-RT, right frontal - right temporal; RT-RP, right temporal - right parietal; RP-RO, right parietal - right occipital; LF-LF, left frontal - left frontotemporal; LT-LP, left temporal - left parietal; LP-LO, left parietal - left occipital; RA, right amygdala; LA, left amygdala; RH, right hippocampus; PRF, pontine reticular formation; and EM, eye movements.

Fig. 2.   C. Drowsy state. Behavioral concomitants are occasional

blinking movements of the closed lids.   D.   Representative

section of light sleep from early evening.

Fig. 3. E. Intermediate sleep. Predominantly slow activity with preservation of some faster frequencies. F. Deep sleep. Predominantly high voltage slow activity.

Fig. 4. Average percentage of time spent in various sleep stages.
Vertical lines indicate scatter.

Fig. 5. Representative night's sleep pattern. Paradoxical sleep is
         cross-hatched and occurred predominantly in the early
         morning. Deep sleep (stippled) occurred mainly in the
         early part of the night.

Fig. 6. Alerting stimulus, demonstrating activation in deep structures prior to cortical changes. The noise occurred approximately two seconds before the eyes opened (arrow). An increase in fast activity occurred in the pontine reticular formation, then the limbic structures and finally the cortical areas.

Fig. 7. A. Characteristic drowsy period late in evening.

B. Typical paradoxical sleep record with intervening

periods that resemble drowsy records.

Fig. 8. Variations in responsiveness of various structures to click

stimuli during different stages of sleep. Note in particular

the progression of increased amplitude in the cortical

response during deep sleep as contrasted with the response

of the amygdala electrode.